Long-term Multi-product Facial Regimen in Subjects with Moderate-to-severe Photodamage and Hyperpigmentation

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ABSTRACT

Background: Photoaged skin is primarily a result of chronic sun exposure. Irregular pigmentation and wrinkling are common clinical manifestations. Monotherapy with retinoids, growth factors, and skin lighteners have proven beneficial. However, long–term treatment with a multi-product facial regimen has not been assessed. **Objectives:** This single-center clinical trial was conducted to assess the efficacy and tolerance of a topical multi-product regimen when used by subjects with moderate-to-severe photodamage and hyperpigmentation on the face over a course of 24 weeks. **Methods:** Subjects were supplied with a six-product regimen to use on their face (cleanser, growth factor serum, skin brightener, moisturizer, retinol, and sunscreen). Products were used according to specific application instructions. Clinical grading and tolerability assessments were performed at baseline and at follow-up visits at Weeks 4, 8, 12, 18, and 24. Standardized digital photographs were taken and self-assessment questionnaires were conducted. Image analysis for skin-tone evenness and brightness was also conducted. **Results:** Seventy-two subjects completed the 24-week study. All clinical efficacy parameters showed statistically significant improvements over baseline at all visits. Plateau effects for these improvements were not seen at 24 weeks. The facial regimen was well-tolerated. Subject questionnaires showed the regimen was highly rated at all visits. **Conclusion:** This six-product, comprehensive facial regimen was shown to be clinically effective and well-tolerated for the treatment of moderate-to-severe photodamage and hyperpigmentation over 24 weeks. Additional benefits may occur with continued use. (*J Clin Aesthet Dermatol.* 2015;8(8):16–21.)

Photoaging of human skin is primarily due to chronic exposure to ultraviolet radiation. This premature aging in the appearance and function of the skin is cumulative over time and is dependent on the degree and intensity of exposure to the sun along with the skin's natural pigment.[1,2] Photoaged skin is characterized by various clinical manifestations, including coarseness; wrinkling; irregular pigmentation; laxity; telangiectasia; lentigines; atrophy; purpura; and various benign, premalignant, and malignant neoplasms on the face, neck, hands and other areas of the body chronically exposed to the sun. Uneven pigmentation is often a prominent feature in sun-exposed skin.[3–5] Dyspigmentation can cause considerable aesthetic concerns, as well as psychosocial distress, in affected individuals.[6] As such, many seek treatment for their irregular pigmentation as well as other manifestations of photodamaged skin.

The efficacy of topical retinoids in the treatment of photoaged skin, including dyspigmentation, is well known.[7–10] Likewise, the use of certain anti-aging products containing growth factors has been shown effective in photoaging.[11–14] Hydroquinone-free skin lightening agents have shown benefit in treating dyschromia due to various etiologies.[15–18] However, a comprehensive facial regimen containing all three modalities along with a basic skincare regimen of a cleanser, moisturizer, and sunscreen has not been formally studied. This clinical trial is designed to assess the effects of long-term treatment with this comprehensive facial regimen on subjects with both moderate-to-severe photodamage and hyperpigmentation.

MATERIALS AND METHODS

Seventy-four subjects (aged 30 years or older) with

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Fitzpatrick skin type I to IV in good general health with both moderate-to-severe facial photodamage and facial hyperpigmentation were included in the intent-to-treat (ITT) population. Subjects were required to have a baseline score of 4 or greater on both the Investigator's Overall Photodamage scale and the Investigator's Overall Hyperpigmentation scale.

Subjects were provided with a facial regimen of six products (Facial Cleanser, TNS Essential Serum®, Lytera® Skin Brightening Complex, Retinol Complex 0.5, Rejuvenative Moisturizer and Daily Physical Defense® SPF30+, SkinMedica, Inc.) along with usage instructions. See Table 1 for the application regimen for these products.

Institutional Review Board approval was obtained prior to commencement. This study was conducted according to ethical and regulatory principles from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Prior to treatment, subjects provided informed consent. The study was conducted in Dallas, Texas, from August 2013 to February 2014.

Subjects were treated over a 24-week period with visits at baseline, Week 4, Week 8, Week 12, Week 18, and Week 24. Subjects arrived at the clinic having removed all makeup prior to the visit and had the following assessments at each visit:

Clinical efficacy. An expert grader evaluated the face of each subject for the following parameters using a modified Griffiths 10-point scale.[19]

- Overall hyperpigmentation: (0=none, even skin color with no observable hyperpigmentation, 1–3=mild, 4–6=moderate, and 7–9=severe, significant detectable hyperpigmentation appearance, involving most of the face with very strong intensity).
- Overall photodamage: (0=none, no evidence of photodamage; no evidence of lines, wrinkles or mottled/discrete hyperpigmentation), 1–3=mild, 4–6= moderate, and 7–9=severe, pronounced photodamage (numerous deep wrinkles, advanced sagging, and mottled/discrete pigmentation may or may not be present).
- Fine lines/wrinkles—periocular and cheek (0=none, no evidence of fine lines/wrinkles, 1–3=mild, 4–6=moderate, and 7–9=severe, numerous fine lines).
- Coarse lines/wrinkles—priocular and cheek (0=none, no evidence of coarse lines/wrinkles, 1–3=mild, 4–6= moderate, and 7–9=severe, numerous and deep coarse wrinkles).
- Overall skin-tone evenness (0=none, skin is uniform in skin color with perfect evenness, 1–3=mild, 4–6= moderate, and 7–9=severe, skin is uneven and blotchy in tone).
- Tactile roughness—cheek (0=none, skin is completely smooth, 1–3=mild, 4–6=moderate, and 7–9=severe, skin is roughly textured).
- Investigator's global improvement—overall hyperpigmentation: (0=no change or worsening, 1=minimal improvement, 2=mild improvement, 3=moderate improvement, 4=marked or significant improvement).
- Investigator's global improvement—overall photodamage: (0=no change or worsening, 1=minimal improvement, 2=mild improvement, 3=moderate improvement, 4=marked or significant improvement).

TABLE 1. Schedule for application of facial regimen products (GRASS regimen)

Facial Cleanser	Morning	Evening
TNS Essential Serum	Morning	Evening
Lytera Skin Brightening Complex	Morning	Evening
Rejuvenative Moisturizer	Morning	Evening
Daily Physical Defense SPF 30+	Morning and reapply as needed during day	
Retinol Complex 0.5		Evening (apply every other day during initial week)

Tolerability. Each subject was assessed by the investigator for objective evidence of erythema and dryness/scaling using a 4-point scale (0=none, 3=severe). Subjects assessed themselves for irritation parameters including burning, stinging, and itching on a 4-point scale (0=none, 3=severe).

Digital photography. Digital photographs were taken at baseline and at Weeks 4, 8, 12, 18, and 24 using the VISIA CR2 (Canfield Imaging Systems, Fairfield, New Jersey). At each visit, subjects had three sets of full-face images taken (right side, left side, and center view) with standard light 1 and 2 and cross-polarized light with brown channeling.

Image analysis. Digital photographs taken under cross-polarized lighting at baseline and at Weeks 8, 12, 18, and 24 were subjected to image analysis to assess skin-tone evenness and skin brightness. Both analyses were done using proprietary macros developed by Stephens & Associates using Image Pro Plus v7 software (Media Cybernetics, Inc., Rockville, Maryland).

Skin-tone evenness analysis quantifies the variation of color intensity on defined areas of the face and reports skin-tone evenness index, which is defined as the average of (standard deviation)^2/(5*average intensity) of each color channel. Lower index value indicates more even skin tone. For this study, green and blue color channels were considered. The forehead and cheek areas from left view photos were selected for analysis.

For skin brightness analysis the RBG digital images were first converted to CIE Lab color space then the L*

TABLE 2. Demographic information for ITT population

MEAN AGE (RANGE)	GENDER	SKIN TYPE	MEAN BASELINE OVERALL HYPERPIGMENTATION SCORE (RANGE)	MEAN BASELINE OVERALL PHOTODAMAGE SCORE (RANGE)
57.2 years (33–75)	F – 81% M – 19%	II – 16% III – 61% IV – 23%	5.6 (4–8)	6.0 (4–8.5)

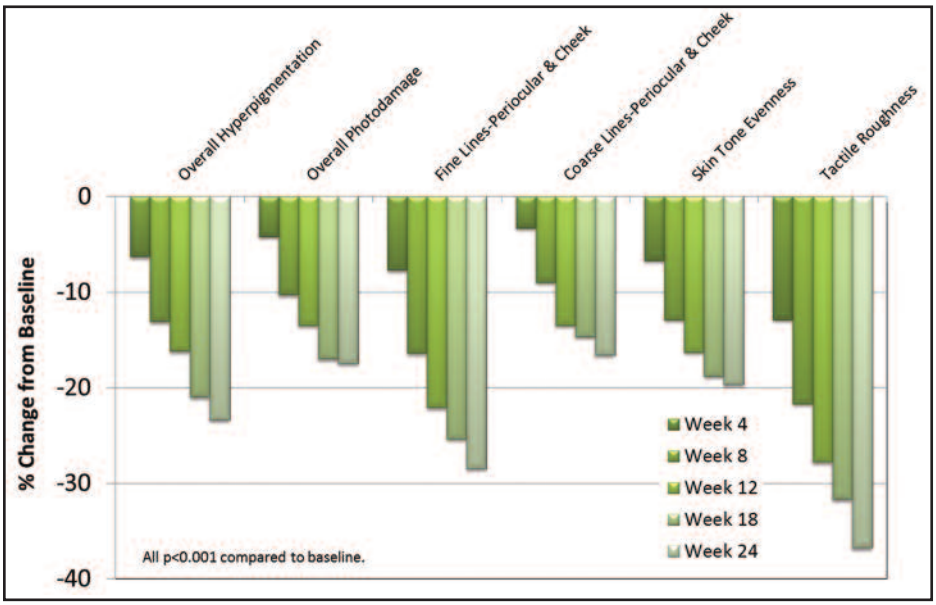

Figure 1. Mean percent changes from baseline in grading scores for all clinical efficacy prameters over 24-week treatment period

values were calculated for selected areas on the face. Higher L* value indicates brighter skin. For this study, two pigmented spots (~1cm diameter each) on the left cheek were selected for analysis.

Self-assessment questionnaires. Subjects completed a self-assessment questionnaire regarding their experience with the facial regimen at Weeks 4, 8, 12, 18, and 24.

Statistical analysis. The ITT population was the primary population for all statistical analyses. The ITT population included all subjects who were randomized and participated in at least one post-baseline evaluation. Wilcoxon signed-rank test was used for Investigator's Global Assessments (overall hyperpigmentation and overall photodamage), clinical grading of the efficacy parameters and tolerance parameters, as well as the parameters from image analysis results. The average percentage change from baseline was calculated at each post-baseline evaluation visit. All differences were considered to be statistically significant at $P<0.05$ level.

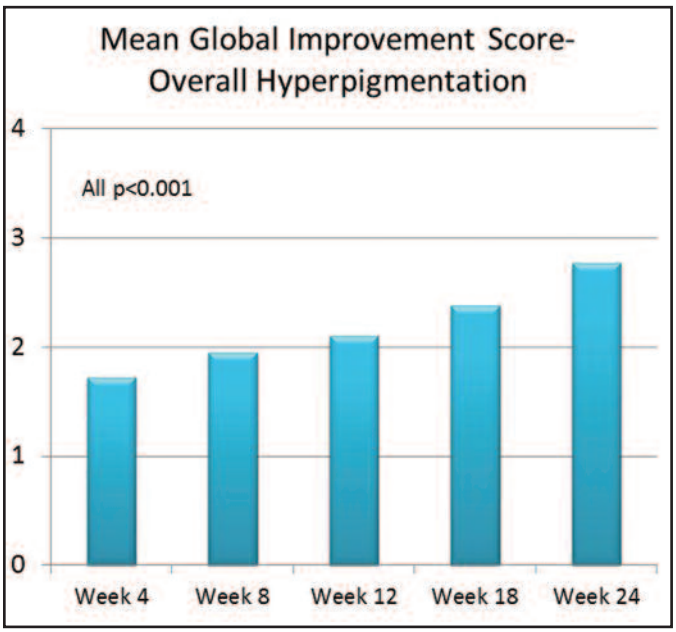

Figure 2. Investigator's global improvement assessment—overall hyperpigmentation over 24-week treatment period

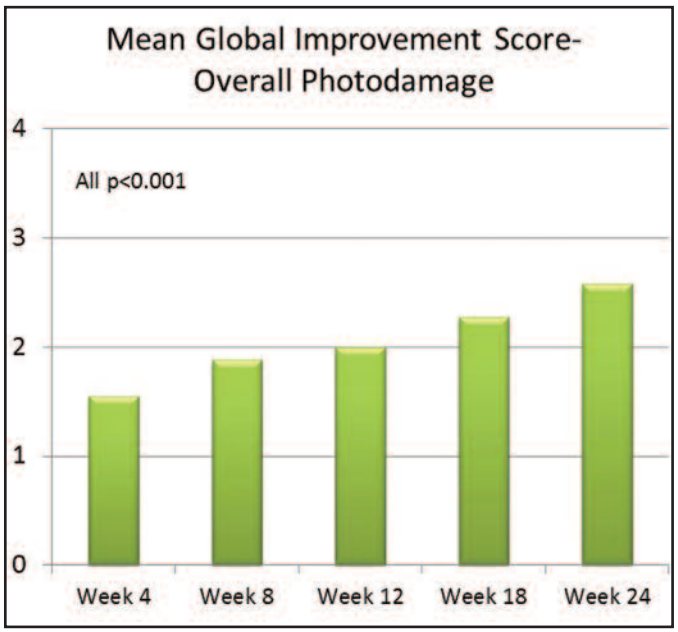

Figure 3. Investigator's global improvement assessment—overall photodamage over 24-week treatment period

RESULTS

The demographic data for the ITT population is presented in Table 2. Seventy-two subjects completed the 24-week trial. Two subjects discontinued (one lost to follow-up and one for a serious adverse event not considered to be related to the treatment regimen). All clinical efficacy parameters (overall hyperpigmentation, overall photodamage, fine lines/wrinkles (periocular and cheek area), coarse lines/wrinkles (periocular and cheek area), overall skin tone evenness, and tactile roughness showed statistically significant improvements over baseline at as early as Week 4 with continued significant reductions through Week 24 (all $P<0.001$) (Figure 1). There was progressive improvement over time without a plateau effect for these efficacy parameters over the 24 weeks of treatment. Statistically significant improvements were also observed in the investigator's global improvement assessments for both overall photodamage and overall hyperpigmentation ($P<0.001$) (Figure 2 and 3, respectively).

Digital images captured during the course of the study were subjected to image analysis to obtain objective and quantitative assessments. Skin-tone evenness index showed statistically significant improvement over the course of 24-week treatment (Figure 4). An average of a 16.7-percent improvement for ITT population was observed with 93.1 percent of subjects showing improvement after 24 weeks of product usage. This result is consistent with clinical grading results. Skin brightness, which focuses on the dark spots on the cheek, also showed statistically significant improvement over the course of the 24-week treatment and 98.6 percent of subjects demonstrated improvement.

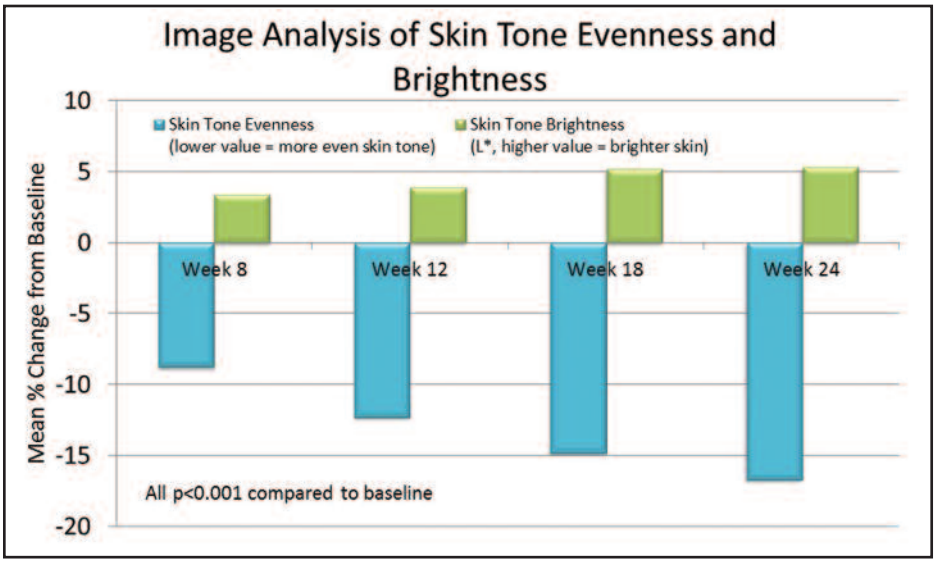

Figure 4. Image analysis of skin-tone evenness and skin-tone brightness

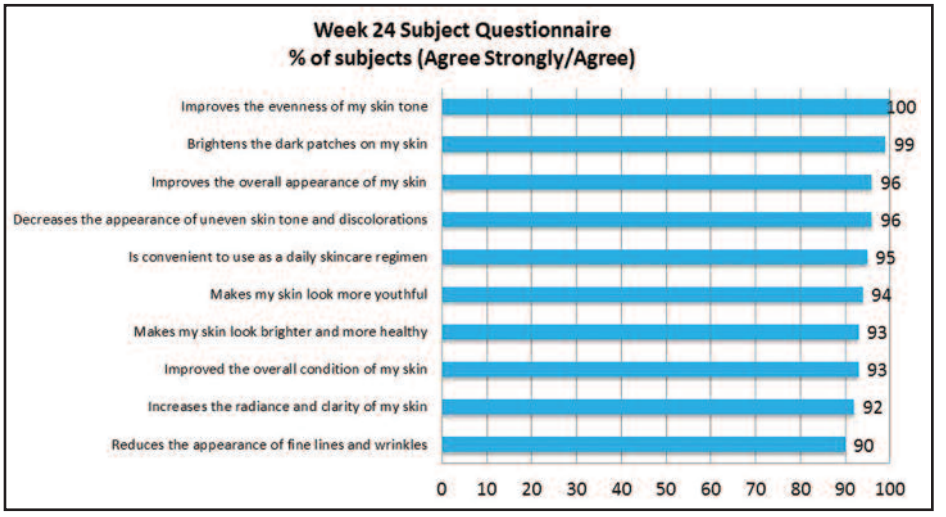

Figure 5. Self-assessment questionnaire results at week 24

The regimen was generally well-tolerated with mean scores for erythema, dryness/scaling, burning, stinging, and itching all scored as less than "mild" for all visits. A statistically significant worsening of burning and stinging on the face was seen at Week 4 compared to baseline. However, the change was very small (<0.12 increase in mean score) and the effect did not persist beyond Week 4 time point. During the first four weeks, subjects who experienced burning/stinging were instructed to reduce application frequency of the retinol complex 0.5 to every other night until the symptoms subsided and resume to daily application. In addition, a significant improvement in mean erythema scores compared to baseline was observed at Weeks 4 through 24.

In the subject questionnaire, 90 percent or more "agreed" or "agreed strongly" with the statements regarding the facial regimen (Figure 5). At Week 24, 96 percent of subjects agreed that the regimen improved the overall appearance of their skin. Figures 6 to 8 illustrate the effects of treatment over 24 weeks of regimen usage.

DISCUSSION

The facial treatment regimen studied, known by the acronym GRASS, refers to growth factors, retinol, antioxidants, specialty products, and sunscreen. Although each of these product types have been individually tested in previous clinical studies,[7–18] the combination of products has not been previously evaluated in a formal clinical study. An additional uniqueness of this study is the duration; very few

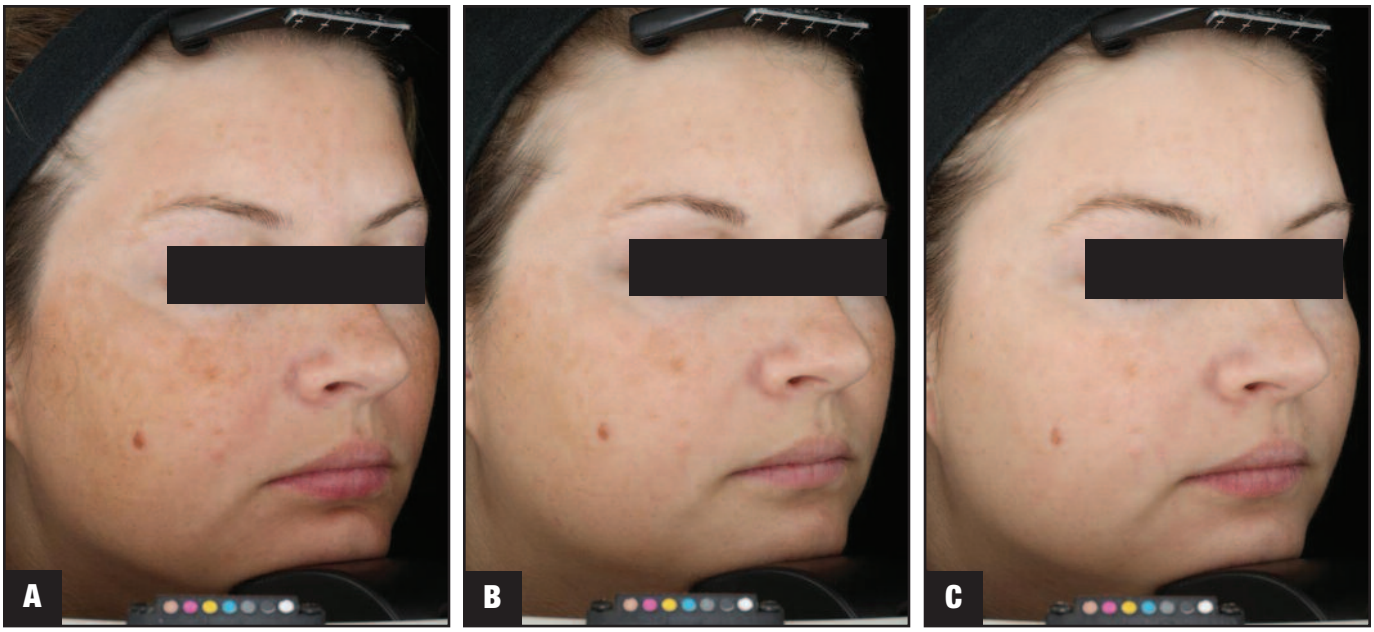

Figure 6. A 35-year-old woman (Fitzpatrick skin type III) at baseline (A), after eight weeks (B), and after 24 weeks (C) of treatment with the multi-product regimen

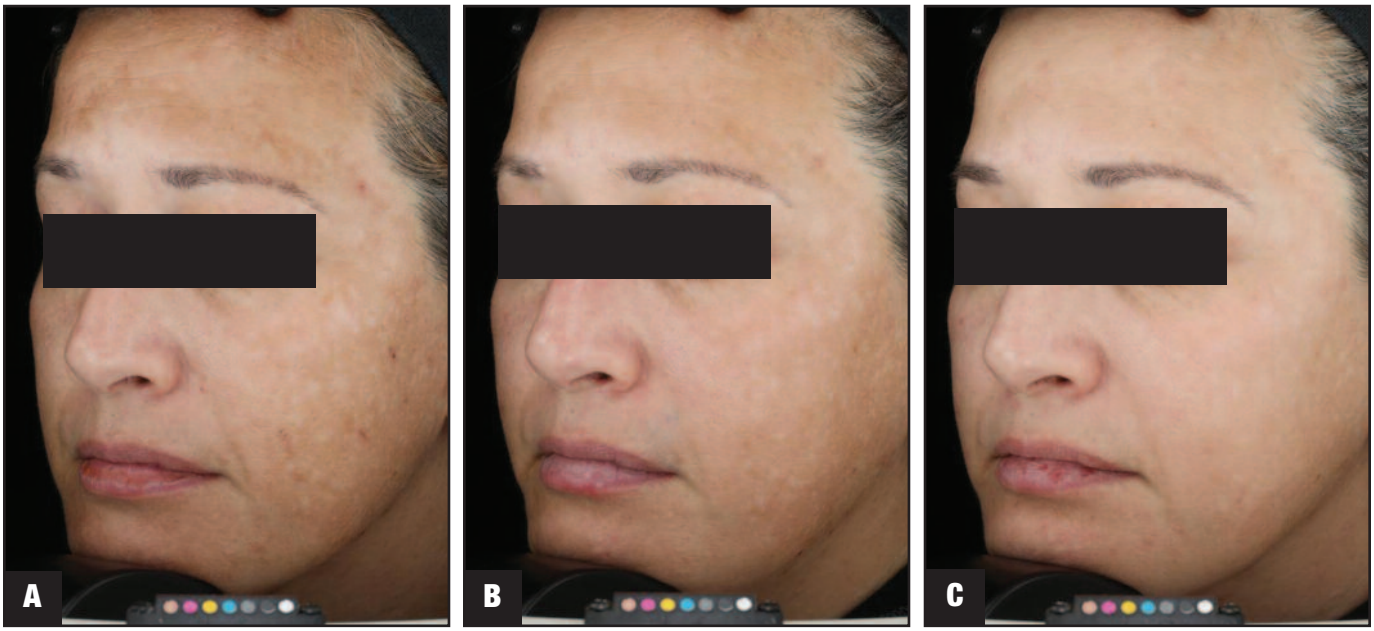

Figure 7. A 35-year-old woman (Fitzpatrick skin type III) at baseline (A), after 12 weeks (B), and after 24 weeks (C) of treatment with the multi-product regimen

studies on cosmetics have been carried out to 24 weeks.

The subjects in this study had both moderate-to-severe photodamage as well as moderate-to-severe hyperpigmentation of the face. Impressive was the finding that all of the measured clinical efficacy endpoints showed a statistical improvement at the first evaluation visit (Week 4) with continued progressive improvement out to 24 weeks. No plateau in response was seen during the 24-week treatment period. The mean changes in Global Improvement Assessments for both overall hyperpigmentation and overall photodamage showed minimal-to-mild improvement after four weeks of treatment, which increased to mild-to-moderate improvement at 24 weeks. These progressive improvements over time without achievement of an efficacy plateau suggests that additional benefits may occur with continued longer term use.

In addition to efficacy, a facial regimen must be safe and well-tolerated. Tolerability assessments by both the investigator and subject confirmed that the treatment regimen was generally well-tolerated. The statistical increase in facial burning and stinging with the facial regimen at Week

4 is not a surprising finding and is typical for a treatment regimen that includes a topical retinoid. Importantly, these symptoms did not persist after the initial Week 4 assessment. It is well known that the most limiting factor with retinoid treatment is skin irritation. This so-called retinoid dermatitis typically occurs during the initial four weeks of treatment and then tends to recede[20] as was seen in this study.

This study demonstrates the benefits of long-term use of a six-product facial regimen for the treatment of moderate-to-severe hyperpigmentation and photodamage. Significant changes were noted at four weeks and progressively improved at each follow-up visit out to 24 weeks.

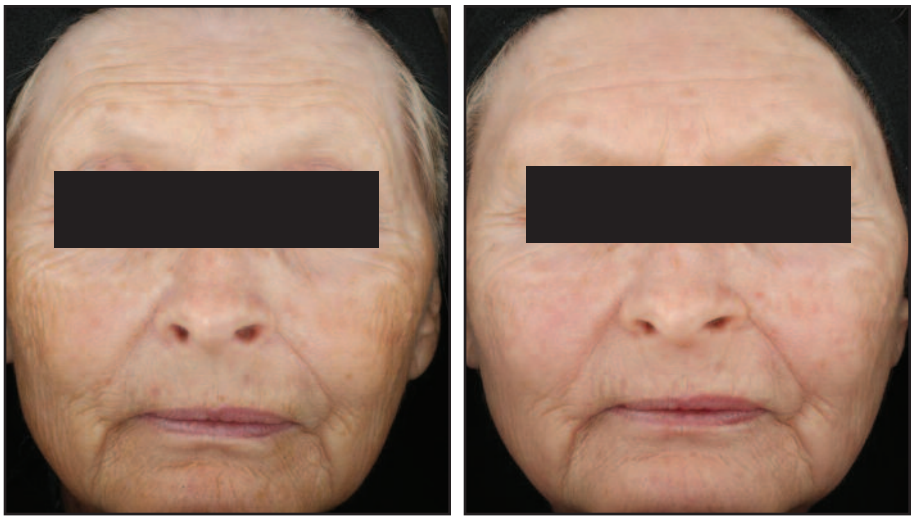

Figure 8. A 65-year-old woman (Fitzpatrick skin type II) at baseline (left) and after 24 weeks of facial regimen (right)

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